

IN THE SPECIFICATION

Please delete paragraph 17 and replace with the following:

[0017] The term "two regions of the β -A4 peptide" relates to two regions as defined by their amino acid sequences shown in SEQ ID NOs: 1 and 2, relating to the N-terminal amino acids 2 to 10 and to the central amino acids 12 to 25 of β -A4 peptide. The term " β -A4 peptide" in context of this invention relates to the herein above described A β 39, A β 41, A β 43, preferably to A β 40 and A β 42. A β 42 is also depicted in appended SEQ ID NO: 27. It is of note that the term "two regions of the β -A4 peptide" also relates to an "epitope" and/or an "antigenic determinant" which comprises the herein defined two regions of the β -A4 peptide or parts thereof. In accordance with this invention, said two regions of the β -A4 peptide are separated (on the level of the amino acid sequence) in the primary structure of the β -A4 peptide by at least one amino acid, preferably by at least two amino acids, more preferably by at least three amino acids, more preferably by at least four amino acids, more preferably by at least five amino acids, more preferably at least six amino acids, more preferably at least nine amino acids and most preferably at least twelve amino acids. As shown herein and as documented in the appended examples, the inventive antibodies/antibody molecules detect/interact with and/or bind to two regions of the β -A4 peptide as defined herein, whereby said two regions are separated (on the primary structure level of the amino acid sequence) by at least one amino acid

and wherein the sequence separating said two regions/"epitope" may comprise more than ten amino acids, preferably 14 amino acids, more preferably 15 amino acids or 16 amino acids. For example, MSR-3 Fab (as an inventive antibody molecule) recognizes detects/interacts with two regions on the β -A4 peptide, wherein said first region comprises amino acids 3 and 4 (EF) and said second regions comprises amino acids 18 to 23 (VFFAED, SEQ ID NO: 421). Accordingly, the separating sequence between the region/epitopes to be detected/recognized has a length of 13 amino acids on the primary amino acid sequence structure. Similarly, MSR #3.4H7 IgG1, an optimized and matured antibody molecules derived from MSR-3 and comprised in an IgG1-framework, detects/interacts with/binds to two epitopes/regions of β -A4 which comprise in the first region positions 1 to 4 (DAEF) and in the second region positions 19 to 24 (FFAEDV, SEQ ID NO: 423) of β -A4 as defined herein. Accordingly, MSR #3.4H7 IgG1 recognizes/detects/interacts with/binds to two epitopes/regions which are, on the primary amino acid sequence level, separated by 14 amino acids. As detailed in the appended examples, affinity maturation and conversion of monovalent inventive Fab fragments to full-length IgG1 antibodies may result in a certain broadening of the epitopes/regions detected in pepspot, ELISA assays and the like. Therefore, the antibody molecules of the invention are capable of simultaneously and independently recognizing two regions of the β -A4 peptide/A β 4 wherein said regions comprise the amino acid sequence as

shown in SEQ ID NO: 1 (or parts thereof) and the amino acid sequence as shown in SEQ ID NO: 2 (or (a) part(s) thereof). Due to the potential broadening of epitopes as detailed herein it is, however, also envisaged that amino acids in close proximity to the sequences of SEQ ID NO: 1 and 2 are detected/recognized, i.e. that additional amino acids are part of the two regions to be detected/recognized. Accordingly, it is also envisaged that, e.g. the first amino acid of A β (1-42) as defined herein, namely D (Aspartic acid) in part of one epitope to be detected/recognized or that amino acids located after the region of A β (1-42) as defined in SEQ ID NO: 2 are detected/recognized. Said additional amino acid may, e.g., be the amino acid on position 26 of SEQ ID NO: 27 (β A4/A β (1-42)), namely S (Serine).

Please delete the last three sentences of paragraph 18 and replace with the following three sentences:

-- Preferred fragments or parts are in the first region/stretch of SEQ ID NO: 27 the amino acid sequences AEFRHD (SEQ ID NO: 415), EF, EFR, FR, EFRHDSG (SEQ ID NO: 416), EFRHD (SEQ ID NO: 417) or HDSG (SEQ ID NO: 418), and in the second region/stretch of SEQ ID NO: 27 the amino acid sequences HHQKL (SEQ ID NO: 419), LV, LVFFAE (SEQ ID NO: 420), VFFAED (SEQ ID NO: 421), VFFA (SEQ ID NO: 422) or FFAEDV (SEQ ID NO: 423). As mentioned above, said fragments may also comprise additional amino acids or may be parts of

the fragments defined herein. Specific examples are DAE, DAEF, FRH or RHDSG. --

Please delete paragraph 37 and replace with the following paragraph:

--[0037] In a preferred embodiment, the antibody molecule of the invention recognizes at least two consecutive amino acids within the two regions of A β 4 defined herein, more preferably said antibody molecule recognizes in the first region an amino acid sequence comprising the amino acids: AEFRHD (SEQ ID NO: 415), EF, EFR, FR, EFRHDSG (SEQ ID NO: 416), EFRHD (SEQ ID NO: 417) or HDSG (SEQ ID NO: 418), and in the second region an amino acid sequence comprising the amino acids: HHQKL (SEQ ID NO: 419), LV, LVFFAE (SEQ ID NO: 420), VFFAED (SEQ ID NO: 421), VFFA (SEQ ID NO: 422) or FFAEDV (SEQ ID NO: 423). Further fragments or broadened parts comprise: DAE, DAEF, FRH or RHDSG.--

Please add the following sentence to the end of paragraph 169:

-- The V_H DNA sequence of the IgG of antibody molecule 7.9H7 after subcloning is shown in SEQ ID No.: 424, and the corresponding amino acid sequence is shown in SEQ ID No: 425.

Please delete paragraph 206 and replace with the following paragraph:

-- [0206] Employing specific of the above described heptapeptides derived from A β , specific ELISA-tests as described herein above were carried out. Preferably, inventive antibodies comprise antibodies which show, as measured by of optical densities, a signal to background ratio above "10" when their reactivity with an A-beta derived peptide (AEFRHD, SEQ ID NO: 415; amino acid 2 to 7 of A-beta) is compared to an non-related protein/peptide like BSA. Most preferably, the ratio of optical densities is above "5" for a corresponding reaction with at least one of the following three A β derived peptides: (VFFAED, SEQ ID NO: 421; amino acid 18 to 23 of A β) or (FFAEDV, SEQ ID NO: 423; amino acid 19 to 24 of A β) or (LVFFAE, SEQ ID NO: 420; amino acid 17 to 22 of A β). --

Please delete the first row of Table 6 and replace with the following language:

--Reactivity of MS-R Fabs with BSA-conjugated, Abeta heptapeptides 2-7 (AEFRHD, SEQ ID NO: 415), 17-22 (LVFFAE, SEQ ID NO: 420), 18-23 (VFFAED, SEQ ID NO: 421) and 19-24 (FFAEDV, SEQ ID NO: 423). The ratios of the ELISA read-out (optical density) obtained with peptide-conjugated and non-conjugated BSA are given. The signal intensities obtained with the 17-22, 18-23 and 19-24 peptides in relation to the 2-7 peptide are also indicated. --

Please delete paragraph 208 and replace with the following paragraph:

-- [0208] Table 6: Reactivity of MS-R Fabs with BSA-conjugated Abeta heptapeptides 2-7 (AEFRHD, SEQ ID NO: 415), 17-22 (LVFFAE, SEQ ID NO: 420), 18-23 (VFFAED, SEQ ID NO: 421) and 19-24 (FFAEDV, SEQ ID NO: 423). The ratios of the ELISA read-out (optical density) obtained with peptide-conjugated and non-conjugated BSA are given. The signal intensities obtained with the 17-22, 18-23 and 19-24 peptides in relation to the 2-7 peptide are also indicated. --

Please delete paragraph 209 and replace with the following paragraph:

-- [0209] Table 7: Reactivity of MS-R IgGs and mouse monoclonal antibodies BAP-1, BAP-2, 4G8, 6E10 Amy-33 and 6F/3D with BSA-conjugated A β heptapeptides 2-7 (AEFRHD, SEQ ID NO: 415), 17-22 (LVFFAE, SEQ ID NO: 420), 18-23 (VFFAED, SEQ ID NO: 421) and 19-24 (FFAEDV, SEQ ID NO: 423). The ratios of the ELISA read-out (optical density) obtained with peptide-conjugated and non-conjugated BSA are given. The signal intensities obtained with the 17-22, 18-23 and 19-24 peptides in relation to the 2-7 peptide are also indicated. *this antibody is specific for sequence 8-17 and does not recognize N-terminal or middle epitope sequences. --

In Column 2, Row 1 of Table 7, please insert "(SEQ ID NO: 415)" after "AEFRHD." In Column 3, Row 1 of Table 7, please insert "(SEQ ID NO: 420)" after "LVFFAE." In Column 4, Row 1 of Table 7, please insert "(SEQ ID NO: 421)" after "VFFAED". In Column 5, Row 1 of Table 7, please insert "(SEQ ID NO: 423)" after "FFAEDV".

Please cancel the Sequence Listing as filed in the original application.

Please enter the Substitute Sequence Listing set forth in Exhibit 1 on the next page after the Abstract.